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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/965,116	09/26/2001	Ekambar R. Kandimalla	HYZ-479CP (47508.577)	3956

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EXAMINER	
LE, EMILY M	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 10/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/965,116	KANDIMALLA ET AL.	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-8 and 39-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-8 and 39-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 3.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/11/2005 has been entered.

Status of Claims

2. Claims 4-5 and 9-38 are cancelled. Claims 39-43 are added. Claims 1-3, 6-8 and 39-43 are pending and under examination.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

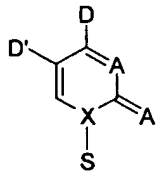
> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-3, 7-8 and 42 remain rejected under 35 U.S.C. 102(a) as being anticipated by Schwartz.

The claims are directed to an oligonucleotide compound comprising a dinucelotide of formula 5'-pyriminde-purine-3', wherein the compound is at least 6 nucleotides in length, and wherein the pyrimidine is a non-natural pyrimidine nucleoside

selected from the group consisting of 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine, aracytosine, and 4-thiouracil; and the purine is guanosine—a natural purine, or non-natural purine nucleoside, wherein the non-natural purine nucleoside is selected from the group consisting of 2-deoxyguanosine, or a guanosine analog.

The claims also require that the pyrimidine be linked to the purine via an internucleotide linkage selected from the group consisting of phosphodiester, phosphorothioate, and phosphorodithioate; the non-natural pyrimidine nucleoside has the formula (I):



(I)

wherein D is a hydrogen bond donor, D' is selected from the group consisting of hydrogen, hydrogen bond donor; hydrogen bond acceptor, hydrophilic group, hydrophobic group and electron donating group; A is a hydrogen bond acceptor or a hydrophilic group, X is carbon or nitrogen, and S is a pentose or hexose sugar ring, provided that he pyrimidine nucleoside of formula (I) is not cytidine or deoxycytidine.

The claims also require the non-natural pyrimidine nucleoside comprises a non-naturally occurring sugar moiety, which is later limited to arabinose or arabinose derivatives; which is later specified as aracytosine.

In response to the rejection set forth in the record, Applicant submits that Schwartz does not place the presently claimed invention in the possession of a person of ordinary skill in the field because Schwartz does not demonstrate the modification of cytosine with anything by a halogen group. Unlike the present application, Schwartz's mere mention of an arabinose sugar modification in a laundry list of possible modifications, with no working example, does not meet the criteria of In re Spada.

Applicant's submission has been considered, however, it is not found persuasive. The Office disagrees with Applicant's position. In the instant, Schwartz teaches that modified cytosine can be anyone of the 19 listed modified cytosines, which includes aracytosine. A listing of 19 different species of modified cytosine among a multitude of modified cytosines is not a laundry list. In the instant, Schwartz clearly envisaged the use of aracytosine as the non-natural pyrimidine.

Additionally, Applicant is reminded that an anticipation analysis is not made on the basis of the decision or opinion that is expressed in *In* re Spada. An anticipation analysis is made on the basis of 35 U.S.C 35 § 102, specifically 102(a) for this rejection. Thus, Schwartz does not have to meet the criteria expressed In re Spada to anticipate the claimed invention.

35 U.S.C § 102 (a) statue states: (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent. The statue clearly states that anticipation occur when the claimed invention is patented or described in a

printed publication in this or a foreign country. In the instant, the claimed invention is described in a printed publication, by Schwartz.

Schwartz teaches an oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the pyrimidine is a non-natural pyrimidine nucleoside and purine is a natural purine nucleoside—guanosine, and that the pyrimidine is linked to the purine via an internucleotide linkage, specifically phosphodiester.

The oligonucleotide compound of Schwartz comprises a non-natural pyrimidine, aracytosine. Aracytosine is not a cytidine or deoxycitidine. Aracytosine has a formula that is in congruence with formula (I), wherein D a hydrogen bond donor, D' is a hydrogen, A is a hydrogen bond acceptor, S is a pentose sugar ring, and X is nitrogen. The pentose sugar ring of aracytosine is a non-naturally occurring sugar moiety, particularly arabinose. [Claim 4 of Schwartz]

In the instant, Schwartz teaches the same oligonucleotide compound as that instantly claimed. Ergo, Schwartz anticipates the claimed composition.

5. Claims 1-3, 7 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Zuo et al.

The significance of claims 1-3 and 7 is provided above. Claim 40 requires the non-natural pyrimidine nucleoside be 5-hydroxycytosine.

In response to the rejection set forth in the record, Applicant submits that Zuo et al. does not deal with immunostimulatory oligonucleotides and their administration. Applicant contends that one of ordinary skill in the art would not understand that Zuo et

al. is discloses an immunostimulatory oligonucleotide. Thus, Zuo et al. does not anticipate the claimed invention.

Applicant's submission has been considered, however, it is not found persuasive. In the instant, Zuo et al. teaches the same composition as claimed. Zuo et al. teaches an oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the pyrimidine is a non-natural pyrimidine nucleoside and purine is a natural purine nucleoside. The compound of Zuo et al. can also be defined as C*pG, wherein C* is a cytidine analog, G is guanosine, and p is an internucleotide linkage--phosphodiester. The oligonucleotide compound taught by Zuo et al. comprises a non-natural pyrimidine, 5-hydroxycytosine, which comprises the following characteristic: i) the 5th position, which is a carbon, is linked to a hydrogen bond donor, which is also a hydrophilic group and an electron donating group; ii) the 4th position, which is a carbon, is linked to a hydrogen bond donor; iii) the 3rd carbon position is a hydrogen bond acceptor and is a hydrophilic group; iv) the 2nd and 3rd carbon position is a hydrogen bond acceptor and is a hydrophilic group; v) the 1st position is a nitrogen; and v) the group attached to the 1st position is a pentose sugar ring. The non-natural pyrimidine nucleoside in the oligonucleotide compound taught by Zuo et al. is not cytidine or deoxycitidine--natural pyrimidine nucleosides. The composition of Zuo et al. is the same as the claimed composition. Thus, Zuo et al. anticipates the claimed invention.

Applicant is reminded that Zuo et al. does not need to recognize or demonstrate that the composition is immunostimulatory to anticipate the claimed invention. Such is in accordance with the guidance provided in MPEP § 2112 (II), which states that the

prior art does not need to recognize the inherent property of the composition to anticipate the claimed invention. In the instant, immunostimulatory properties are intrinsic to the composition itself. Thus, the composition of Zuo et al. would necessarily have immunostimulatory properties.

6. Claims 1-3, 7 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Butkus et al.

The relevance of claims 1-3 and 7 are discussed above. Claim 41 limits the non-natural pyrimidine to N4-alkylcytosine.

In response to the rejection set forth in the record, Applicant submits that Butkus et al. does not deal with immunostimulatory oligonucleotides and their administration. Applicant contends that one of ordinary skill in the art would not understand that Butkus et al. is discloses an immunostimulatory oligonucleotide. Thus, Butkus et al. does not anticipate the claimed invention.

Applicant's submission has been considered, however, it is not found persuasive. In the instant, Butkus et al. teaches the same composition as claimed. Butkus et al. teaches a CpG composition that comprises an unnatural pyrimidine, wherein the unnatural pyrimidine is N4-methylcytosine. N4-methylcytosine is an N4-alkylcytosine. The CpG composition of Butkus et al. is the same as the claimed invention. Ergo, Butkus et al. anticipates the claimed invention.

Butkus et al. does not need to recognize or demonstrate that the composition is immunostimulatory to anticipate the claimed invention. Such is in accordance with the guidance provided in MPEP § 2112 (II), which states that the prior art does not need to

recognize the inherent property of the composition to anticipate the claimed invention. In the instant, immunostimulatory properties are intrinsic to the composition itself. Thus, the composition of Butkus et al. would necessarily have immunostimulatory properties.

7. Claims 1-3, 6-7 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Kreutzer et al.

The relevance of claims 1-3 and 7 are provided above.

Claim 6 limits the non-naturally occurring pyrimidine base to 5-hydroxycytosine or N4-ethylcystosine. Claim 39 limits the non-naturally occurring pyrimidine base to 5-hydroxycytosine.

In response to the rejection set forth in the record, Applicant submits that Kreutzer et al. does not deal with immunostimulatory oligonucleotides and their administration. Applicant contends that one of ordinary skill in the art would not understand that Kreutzer et al. is discloses an immunostimulatory oligonucleotide. Thus, Kreutzer et al. does not anticipate the claimed invention.

Applicant's submission has been considered, however, it is not found persuasive. In the instant, Kreutzer et al. teaches the same composition as claimed. Kreutzer et al. teaches a CpG composition that comprises an unnatural pyrimidine, wherein the unnatural pyrimidine is 5-hydroxymethylcytosine. The CpG composition of Kreutzer et al. is the same as the claimed invention. Ergo, Kreutzer et al. anticipates the claimed invention.

Kreutzer et al. does not need to recognize or demonstrate that the composition is immunostimulatory to anticipate the claimed invention. Such is in accordance with the

guidance provided in MPEP § 2112 (II), which states that the prior art does not need to recognize the inherent property of the composition to anticipate the claimed invention. In the instant, immunostimulatory properties are intrinsic to the composition itself. Thus, the composition of Kreutzer et al. would necessarily have immunostimulatory properties.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz in view of Bennett et al.

The claims limit the unnatural pyrimidine 4-thiouracil.

In response to the rejection set forth in the record, Applicant submits that Schwarz does not disclose the claimed invention because Schwartz does not meet the criteria of In re Spada. Applicant also submits that Bennett fails to provide that which Schwartz lacks. Bennett et al. does not teach or suggest immunostimulatory oligonucleotides containing the CpG dinucelotide or the administration of such oligonucleotides to affect an immune response. Thus, one of ordinary skill in the art would not have had any motivation to combine the descriptions in Schwartz and Bennett et al. to arrive at the claimed invention. Therefore, the claims are unobvious over Schwartz and Bennett et al.

Applicant's submission has been considered, however, it is not found persuasive. Applicant is reminded that the instant rejection is an obviousness rejection, not an anticipatory rejection. In the instant, Schwartz teaches immunomodulatory oligonucleotide that comprises a central CG sequence, wherein C is a modified cytosine. For a detailed analysis of the teachings of Schwartz, see above.

In the instant, Schwartz does not teach the use of 4-thiouracil as a modified cytosine, a pyrimidine. However, Schwartz teaches that any other modified pyrimidine can be used in place of the modified cytosine that Schwartz teaches to make an immunomodulatory oligonucleotide.

Bennett et al. teaches a comprehensive listing of modified pyrimidine bases, including 4-thiouracil, that can be used in place of the natural pyrimidine base. Bennett et al. clearly provides for the deficiency noted in Schwartz.

In view of the teachings of Schwartz and Bennett et al., it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to substitute known equivalents with one another. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because Schwartz suggests the use of modified pyrimidine in an immunomodulatory oligonucleotide and 4-thiouracil is a modified pyrimidine.

Therefore, one of ordinary of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of producing the claimed invention, absent unexpected results to the contrary.

Note: Applicant is reminded that the instant rejection is directed at claim 43, not claims 5-8 as suggested by Applicant in Applicant's submission.

Conclusion

10. No claim is allowed.

11. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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